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Novel Influenza A (H1N1) infection *vs.* common Influenza-Like Illness: A prospective study

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A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
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F Literature Search
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Summary

Background: On June 11th, 2009 the World Health Organization (WHO) declared the first influenza pandemic of the 21st century. Data regarding the clinical characteristics and course of this viral infectious disease are still being assessed. The aim of this study was to investigate and compare the possible differences in clinical course and outcome between H1N1-positive [H1N1(+)] and negative [H1N1(–)] patients.

Material/Methods: This prospective study was conducted between July 2009 and January 2010 in a regional hospital in Greece. The study population consisted of 165 patients aged 14 years or older, with influenza-like illness (ILI) who, according to CDC recommendations, fulfilled the criteria for diagnostic influenza testing. Enrolled patients underwent a detailed diagnostic work-up. Infection by the H1N1 virus was diagnosed using real-time reverse transcriptase polymerase chain reaction, from pharyngeal swab specimens.

Results: We identified 81 H1N1 (+) (49%) patients. Statistical analysis revealed that H1N1(+) patients were significantly younger (median age 27 *vs.* 35 years, $p<0.05$), had a decreased white blood cell count (median 7.200 *vs.* 8.415, $p<0.05$) and an increased percentage of monocytes (55.6% *vs.* 27.4%, $p<0.05$) compared to the H1N1(–) patients. The clinical presentation at the emergency department, as well as the hospital admission and disease complication rate, were not significantly different between the 2 groups.

Conclusions: The clinical characteristics of the new influenza virus appear to be mild and to resemble those of common influenza-like illnesses (ILI). The patients who tested positive for the H1N1 virus were younger and had an increased percentage of monocytes compared to the H1N1-negative patients.

key words: **H1NI • influenza virus • infections**

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Background

On June 11th, 2009 the World Health Organization (WHO) declared the first influenza pandemic of the 21st century. The culprit is a distant descendant of the influenza A H1N1 virus, first known to occur in 1918 [1]. This novel strain is a reassortant virus consisting of 1 avian and 1 human strain, and 2 swine strains of influenza [2]. Unlike its predecessors, it has reached pandemic proportions in quite a short time [3]. According to the WHO, as of March 2010, more than 213 countries have reported laboratory-confirmed cases of pandemic influenza H1N1, including at least 16,713 deaths worldwide [4]. The most active areas of infection are currently in Southeast Asia, while in Europe transmission rates appear to have declined. Presently, data on the clinical characteristics and course of the 2009 H1N1 virus are still under scrutiny. With the aim of adding to the growing body of literature on this influenza pandemic, this prospective study investigated and compared the clinical characteristics and outcomes of H1N1-positive patients and compares them to H1N1-negative patients.

Material and Methods

This prospective study was conducted during a 7-month period between July 2009 and January 2010, and patients were identified on a random basis in the emergency department of a regional hospital in Greece, located in the city of Argos, in the province of Argolida. This province is close to the capital, and its current population is approximately 106,000 people, which on summer months and weekends increases to more than 150,000. The study protocol was approved by the hospital's Ethics Committee.

The study population consisted of 165 patients aged 14 years or older (no pediatric patients were included) with influenza-like illness (ILI) who, according to CDC recommendations, fulfilled the criteria for diagnostic influenza testing. Influenza-like illness was defined by the presence of fever, sore throat, cough, or all 3 of these, in the absence of another known cause. Patients with symptoms of the illness were subjected to laboratory testing in order to identify H1N1 infection. Informed consent was obtained from all patients before study enrollment.

Enrolled patients underwent a detailed diagnostic workup, including case history, physical examination, chest x-ray, complete blood cell count, and laboratory chemical evaluation of liver and kidney function, as well as electrolyte evaluation. Data on the patients' age, prior medical history and present signs and symptoms were recorded in a standardized case report form. Infection by the H1N1 virus was diagnosed by real-time reverse transcriptase polymerase chain reaction (rRT-PCR). Pharyngeal swabs were obtained and placed into sterile viral transport medium and immediately placed in a 4°C environment for transport to the central laboratory. Based on the rRT-PCR results, patients were classified as H1N1-positive or H1N1-negative. Admission to the hospital was based on the degree of respiratory distress, persistence of fever, and the presence of infiltrates in the chest x-ray. The patients were discharged on advice of medical treatment or admitted to the Internal Medicine ward for further treatment. All patients (admitted or discharged) were closely monitored until complete resolution of their symptoms.

A standard statistical software package, SPSS (SPSS Inc, Chicago, IL), was used in the analysis. Descriptive statistics were calculated for all variables. Categorical variables were analyzed with the chi-square test or Fisher's exact test, as appropriate. The 1-sample Kolmogorov-Smirnov test was used to test whether a variable was normally distributed. Normally distributed data were analyzed with the T-test, while in the absence of normal distribution, the Mann-Whitney test was used. Normally distributed data are shown as mean ±SD, while in the absence of normal distribution values are presented as medians [25th, 75th percentile]. P values less than 0.05 were considered statistically significant.

Results

A total of 83 male and 82 female patients with a median age of 32 [range: 20–48] were enrolled during the 7-month study period. Initial presentations included sore throat in 45.5%, rhinorrhoea in 35.1%, dyspnea in 23.4%, cough in 72.7%, myalgias in 46.8%, headache in 35.1%, diarrhea in 10.4% and vomiting in 7.8% of the study population. Measurement of complete blood count revealed that 67.3% had normal leukocyte counts (4.000–11.000/mL), 11.5% had leukopenia and 41.2% had an elevated percentage of monocytes (>9%). Thirty-three percent of the patients were admitted to the internal medicine ward and 13.3% had infiltrates in their chest X-rays. The mean duration of the patients' symptomatic illness was 5 days.

Based on the rRT-PCR results from the pharyngeal swab specimens, 81 H1N1 (+) (49%) patients were identified. Their average age was 33 years, with a standard deviation of 17.23 years. The minimum age was 14 years and the maximum age was 76 years. The median age in our study was 27 years. Eleven of the H1N1(+) patients (13.8%) had traveled abroad in countries with established pandemic status, 26 (32.5%) had been in close contact with a verified case of H1N1 infection, and the rest (53.8%) had no history of obvious contact with infected people. Eight out of 9 members, from 3 unrelated families, who were tested for the new influenza virus, were found to be positive for the H1N1 virus. Furthermore, 1 middle-aged female patient was diagnosed with H1N1 infection even though she had received the 2009 monovalent vaccine 2 months prior to the diagnosis.

Statistical analysis revealed that the H1N1(+) patients were significantly younger (median 27 *vs.* 35 years, $p<0.05$), had a decreased white blood cell count (median 7.200 *vs.* 8.415, $p<0.05$) and an increased percentage of monocytes (55.6% *vs.* 27.4%, $p<0.05$) compared to the H1N1(–) patients. The clinical characteristics of the population examined in the emergency room setting and the rate of disease complications compared to the rates in the patients admitted to the hospital ward were not significantly different between the 2 groups (Table 1).

Discussion

After the global spread of the new swine-origin influenza virus A (H1N1), many countries, including Greece, organized a network for the report, diagnosis and treatment of influenza A (H1N1) infection. Our hospital is based in Argos, a Greek city of 25,000 people. The province's health care system provides primary medical care in small rural medical

Table 1. Patients' clinical and laboratory data.

	H1N1(–) (N=84)	H1N1(+) (N=81)	P VALUE
Age (median [IQR])	35 [24,48]	27 [18,45]	<0.05
WBC(median [IQR])	8.415 [6.470,11.467]	7.200 [5.120,9.615]	<0.05
Duration of Illness(days)(mean ±SD)	4.86±1.48	5.18±1.85	NS
Gender (male/female)	46/38 (54.8%/45.2%)	37/44 (45.7%/54.3%)	NS
WBC			
Normal	56 (66.7%)	55 (67.9%)	NS
High	22 (26.2%)	13 (16%)	
Low	6 (7.1%)	13 (16%)	
Neutrophilles percentage			
Normal	48 (57.1%)	58 (71.6%)	NS
High	32 (38.1%)	18 (22.2%)	
Low	4 (4.8%)	5 (6.2%)	
Lymphocytes percentage			
Normal	40 (47.6%)	44 (54.3%)	NS
High	10 (11.9%)	8 (9.9%)	
Low	34 (40.5%)	29 (35.8%)	
Monocytes percentage			
Normal	61 (72.6%)	36 (44.4%)	<0.05
High	23 (27.4%)	45 (55.6%)	
Hospital admission(no/yes)	59 (70.2%)/25 (29.8%)	52 (64.2%)/29 (35.8%)	NS
Pneumonia (no/yes)	71 (84.5%)/13 (15.5%)	72 (88.9%)/9 (11.1%)	NS
Sore throat	39.5%	51.3%	NS
Rhinorrhoea	28.9%	41.0%	NS
Dyspnea	21.1%	25.6%	NS
Cough	68.4%	76.9%	NS
Myalgias	39.5%	53.8%	NS
Headache	36.8%	33.3%	NS
Diarrhea	15.8%	5.1%	NS
Vomiting	10.5%	5.1%	NS

WBC – White Blood Cells; NS – not statistically significant.

centers where general practitioners or physicians without a specialty offer medical services, while secondary care services are provided by hospitals located in Argos and the provincial capital, Nafplio.

We found that patients infected by the novel influenza virus had a benign clinical course, with signs and symptoms similar to those of common ILI. Further analysis revealed that cough and generalized muscle aches were the main presenting symptoms of H1N1 infection, and hospital admission and disease complication rates were not different from ILI.

The average age of H1N1 flu patients was 33 years. Although this is close to that reported from other countries, it is slightly older, a finding that can be attributed to the exclusion of patients younger than 14 years [5,6]. Additionally this study confirmed that, compared to other flu infections, this virus affected a younger population [7–9]. According to previous serologic studies, older individuals, particularly those born before 1930, were more likely to be exposed to previous H1N1-like viruses, demonstrating higher antibody titers against the novel virus compared to younger patients [10]. To date, the role of seasonal flu vaccination in cross-reactive immune response against the 2009 H1N1 virus remains controversial [10–12]. Differences in patients' age distribution could be related to different virus exposure status due to the increased daily activities and personal contacts of younger people.

Although the current pandemic is considered to have a benign clinical course, it is estimated that the new virus causes an average of 6 to 14 deaths per million persons [13]. One of the key elements in dealing with a viral infection of this proportion is an in-depth knowledge of the host immune

responses [14]. In agreement with our results, a recent study by Giamarelos-Bourboulis et al. revealed an increment of monocyte counts [15]. Furthermore, their study showed a selective defect of TNFa and IFNc production from peripheral blood mononuclear cells after stimulation with heat-killed Streptococcus pneumonia, suggesting a predisposition for pneumococcal infections. The patients who tested negative for the H1N1 virus had a higher mean value of white blood cells; nonetheless, their number remained within the normal reference range of our laboratory, thus making it difficult to draw any clear conclusions regarding the clinical value of this finding.

Our study included a middle-aged female patient who was infected by the H1N1 virus despite having received the 2009 monovalent vaccine 2 months prior to diagnosis. This case raises questions regarding the effectiveness of the new vaccine. Thus far millions of people worldwide have received the novel vaccine. According to the Centers for Disease Control and Prevention, health-care workers, pregnant women, persons aged 6 months to 24 years and high-risk adults aged 25 to 64 years were recommended to be the first to receive the influenza A (H1N1) vaccine; but since late September, vaccination has been expanded to the rest of the population [16,17]. To date, published data supports that the pandemic H1N1 vaccines are immunogenic and have an acceptable safety profile, similar to that of the licensed seasonal vaccine [18,19]. Nonetheless, the immunization program is still at an early stage, thus necessitating the need for further research regarding the vaccines' safety and effectiveness [20].

Conclusions

The current pandemic has shaken health systems worldwide, pushing their capabilities to the edge and posing new questions on issues of surveillance and management. According to our results, the clinical characteristics of the new influenza virus appear to be mild and to resemble those of common influenza-like illness. The patients who tested positive for the H1N1 virus were younger and had an increased percentage of monocytes compared to the H1N1-negative patients. As this pandemic continues to unfold, clinicians must stay alert and current with the latest information regarding H1N1 infection.

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